Treatment of melasma

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Treatment of melasma involves the use of a range of topical depigmenting agents and physical therapies. Varying degrees of success have been achieved with these therapies. The Pigmentary Disorders Academy (PDA) undertook to evaluate the clinical efficacy of the different treatments of melasma in order to generate a consensus statement on its management. Clinical papers published during the past 20 years were identified through MEDLINE searches and methodology and outcome assessed according to guidelines adapted from the US Preventive Services Task Force (USPSTF). The consensus of the group was that first-line therapy for melasma should consist of effective topical therapies, mainly fixed triple combinations. Where patients have either sensitivity to the ingredients or a triple combination therapy is unavailable, other compounds with dual ingredients (hydroquinone plus glycolic acid) or single agents (4% hydroquinone, 0.1% retinoic acid, or 20% azelaic acid) may be considered as an alternative. In patients who failed to respond to therapy, options for second-line therapy include peels either alone or in combination with topical therapy. Some patients will require therapy to maintain remission status and a combination of topical therapies should be considered. Lasers should rarely be used in the treatment of melasma and, if applied, skin type should be taken into account. (J Am Acad Dermatol 2006;54:S272-81.)

Melasma is a pigmentary disorder of the face involving the cheeks, forehead, and commonly the upper lip. This condition is more common in women, accounting for 90% of all cases. It appears in all racial types, but occurs more frequently in those persons with Fitzpatrick skin types IV to VI who live in areas of high ultraviolet radiation; sun exposure deepens these hyperpigmented areas. Treatment of melasma involves the use of topical hypopigmenting agents, such as hydroquinone (HQ), tretinoin (RA), kojic acid, and azelaic acid. Physical therapies, such as chemical peels (glycolic acid [GA], trichloroacetic acid [TCA]), laser therapy and dermabrasion, similar to that used in other hyperpigmentary disorders, have also been evaluated with varying degrees of success.

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Abbreviations used:

FA:	fluocinolone acetonide
GA:	glycolic acid
HQ:	hydroquinone
KF:	Kligman's formula
MASI:	Melasma Area and Severity Index
RA:	tretinoin
TCA:	trichloroacetic acid

One aim of the Pigmentary Disorders Academy was to estimate the clinical efficacy of the different treatments of melasma in order to generate a consensus statement on its management. A MEDLINE search was conducted on therapeutic options for melasma. Clinical studies (excluding case studies) that have been published over the past 20 years were reviewed and the data classified according to specific criteria (see below). Subsequent treatment recommendations were generated on the basis of this published clinical evidence and expert opinion.

TOPICAL THERAPIES

Hydroquinone

HQ inhibits the conversion of dopa to melanin by inhibiting the activity of tyrosinase. Other proposed mechanisms of action are inhibition of DNA and RNA synthesis, degradation of melanosomes, and destruction of melanocytes.[1] HQ can cause permanent depigmentation when used at high concentrations for a long period of time. It is commonly used at concentrations ranging from 2% to 5%, the higher concentrations trading off greater efficacy with

greater skin irritation. Adverse effects of HQ include irritant dermatitis, contact dermatitis, postinflammatory pigmentation, ochronosis, and nail bleaching.

Because hydroquinone is a commonly used therapy for melasma, two representative placebo-controlled studies plus one comparative study have been chosen for inclusion in this review. Ennes, Paschoalick, and Mota De Avelar Alchorne[2] reported on the use of HQ 4% in a double-blind, placebo-controlled trial involving 48 patients with melasma on the face. HQ or placebo was applied twice daily for 12 weeks; both contained a sunscreen with a sun protection factor of 30. Evaluation of efficacy was based on clinical observations and photographic evaluations. Total improvement was defined as complete disappearance of the spot; partial improvement as partial disappearance, and failure as no change or worsening. Results indicated total improvement of melasma in 38% of patients treated with HQ as well as partial improvement and no treatment failures in 57% of patients; 5% of patients discontinued therapy. In the placebo group, 8% of patients had total improvement, 58% had partial improvement, but 17% were classified as treatment failures. Both therapies were well tolerated, with no serious adverse events reported. In a more recent placebo-controlled study, HQ 4% was compared with a skin whitening complex consisting of a mixture of uva ursi extract (a competitive inhibitor of tyrosinase that provokes chemical decoloration of melanin), biofermented *Aspergillus* (chelates copper ion needed for tyrosinase activity), grapefruit extract (exfoliative action), and rice extract (hydrating function) in 30 patients over a 3-month period.[3] Treatment evaluation consisted of patient questionnaires and two independent observers. According to the observer evaluations, HQ use resulted in a 77% improvement with a 25% side-effect rate, primarily pruritus, compared with a 67% improvement and 0% side effects with the skin-whitening complex.

A comparative study has recently been completed involving 4% HQ and the triple fixed combination therapy HQ 4%, RA 0.05%, and fluocinolone acetonide (FA) 0.01% (see below).[4] A total of 120 patients were randomized to one of the two treatment arms and treatment was applied for 8 weeks. Efficacy assessments involved the investigator's static evaluation of melasma severity at each visit using a scale from 0, indicating melasma lesions that were very similar to the surrounding normal skin or with minimal residual hyperpigmentation, to 3, severe (markedly darker than the surrounding normal skin). Primary success was defined as a melasma severity score of 0 at week 8. Evaluation of overall improvement was conducted by the investigator at each visit on a scale from 5, completely cleared (100%), to 1, worsening; hyperpigmentation darker than that of baseline melasma. Secondary success was defined as an improvement score between 3 and 5. Overall evaluation by the patient at week 8 involved a scale from 1, excellent, to 4, poor. At baseline, more than 98% of all patients had moderate (grade 2) or severe (grade 3) melasma. At weeks 4, 6 and 8, melasma severity scores were significantly lower in the triple therapy groups than in the hydroquinone group ($P < .003$). Primary success was achieved for 35% of patients (21/60) and for 5.1% of patients (3/59) in the triple therapy and HQ groups, respectively ($P = .0001$). Secondary success was achieved for 73% (44/60) and 49% (29/59) of patients treated with triple therapy and HQ, respectively ($P = .007$). The proportion of patients who considered that the treatment was "excellent" was greater for triple therapy (50%) than for HQ (34%). There were no significant differences between the two treatment groups for the incidence of the reported adverse events.

Retinoids

Tretinoin. Tretinoin (retinoic acid [RA] or vitamin A acid) is thought to have an inhibitory effect on tyrosinase by inhibiting the enzyme's transcription, as well as on dopachrome conversion factor, with a resulting interruption of melanin synthesis.[5] RA reduces hyperpigmentation through the induction of desquamation. Concentrations ranging from 0.05% to 0.1% have been used and the associated side effects are erythema and peeling in the area of application; postinflammatory hyperpigmentation has also been reported.

RA 0.1% has been used to treat melasma in 30 black patients, with results indicating that the average Melasma Area and Severity Index (MASI) score of the tretinoin-treated group decreased by 32% from baseline compared with a 10% decrease in the vehicle control group.[6] Histological examination of treated skin revealed a significant decrease in epidermal pigmentation in the RA group compared with the control group (Table I). Side effects were limited to a mild retinoid dermatitis in 67% of RA-treated patients. Another randomized controlled study of 0.1% RA once daily in 38 Caucasian women indicated that 13 of 19 tretinoin-treated patients (68%) were clinically rated as improved or much improved, compared with 1 of 19 patients (5%) in the vehicle group ($P = .0006$).[7] Significant improvement first occurred after 24 weeks of tretinoin treatment. Colorimetry (an objective measure of skin color) demonstrated a 0.9 unit lightening of tretinoin-treated melasma and a 0.3 unit darkening with vehicle ($P = .01$); these results